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Naproxen pharmacokinetics in patients with rheumatoid arthritis during active polyarticular inflammation

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1 Patients with rheumatoid arthritis often have hypoalbuminaemia as a sign of disease activity. In view of the extensive binding of naproxen to albumin, the pharmacokinetics of total and unbound drug were studied in eight patients and eight healthy male volunteers during chronic intake of 500 mg twice daily.

2 The area under the serum concentration-time curve of total naproxen during a dose interval, AUC (0,12), was smaller in patients (641 ± 101 mg l^{-1} h) than in volunteers (896 ± 85 mg l^{-1} h; $P < 0.0001$). The unbound naproxen AUCu (0,12) was larger in patients (1.9 ± 0.9 mg l^{-1} h) than in volunteers (0.7 ± 0.2 mg l^{-1} h; $P < 0.01$).

3 The higher unbound naproxen concentrations in patients were accompanied by an approxmately 40% increase in apparent clearance/bioavailability (CL/*F*) and a 60% increase in volume of distribution (*V*/*F*).

4 Both CL/*F* and *V*/*F* were inversely correlated with the individual serum albumin concentration ($r = 0.76$, $P < 0.001$; $r = -0.85$, $P < 0.001$, respectively).

5 The high unbound naproxen concentration in the serum of patients with active rheumatoid arthritis and concomitant hypoalbuminaemia is not known to be accompanied by an increase in side effects and may be beneficial if anti-inflammatory effects correlate with unbound drug concentration.

Keywords clinical pharmacokinetics naproxen rheumatoid arthritis hypoalbuminaemia

Introduction

In patients with active rheumatoid arthritis general signs of inflammation are often present, one of the features being a low serum albumin concentration (Baum & Ziff, 1985). The pharmacokinetics of highly albumin bound drugs, such as naproxen, can be expected to differ from normal in patients with hypoalbuminaemia (Koch-Weser & Sellers, 1976; Rowland, 1984). Therefore we studied naproxen pharmacokinetics during chronic therapy at a dosage of 500 mg twice daily in eight patients with rheumatoid arthritis in an active phase of the disease, and compared the results with values obtained in eight healthy male volunteers.

Methods

Eight in-patients, aged 62 ± 3 years (mean ± s.d.), with either classical or definite rheumatoid arthritis according to the criteria of the American Rheumatism Association (Ropes *et al.*, 1958),

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entered the study. The individual values of clinical and laboratory parameters to assess disease activity in each patient and medication data are shown in Table 1. All patients had been taking naproxen 500 mg twice daily (Naprosyne®, tabl. 250 mg, Sarva-Syntex Nederland, Rijswijk, The Netherlands) for at least 14 days before the study. On the day of study the morning dose of any medication other than naproxen was either omitted or postponed until noon. Naproxen 500 mg was given with breakfast. Immediately before ingestion of the drug an indwelling catheter was placed in an antecubital vein and a sample of blood was drawn at time t_0. Further samples were taken 0.5, 1, 1.5, 2, 3, 4, 8, and 12 h after t_0. During this period the freely voided urine was collected. The mean endogenous creatinine clearance was 85 ± 22 ml min^{-1}; a normal value for the age of the patients (Siersbaek Nielsen *et al.*, 1971). The mean serum albumin concentration was 28 ± 2 g l^{-1}. This was measured by the bromocresolgreen method according to Doumas *et al.* (1971). Serum and urine samples were stored at −20° C until analysis.

Eight healthy male volunteers, aged 24 ± 3 years, with a mean serum albumin concentration of 45 ± 2 g l^{-1}, entered the study. They had not taken any drug during at least 1 month preceding the study and no drug intake other than naproxen was allowed.

Naproxen 500 mg was administered twice daily at 08.30 h and 20.30 h. The morning dose of the drug was taken with breakfast. On the fourth day of naproxen intake blood samples were taken and urine collected, as described for the patients.

Measurement of naproxen in samples of serum and urine was by high pressure liquid chromatography and spectrofluorophotometric detection; the coefficient of variation for total serum naproxen (concentration range 20 – 120 mg l^{-1}) was 1.2% (Van Loenhout *et al.*, 1982). The unbound naproxen serum concentration in the samples was determined after equilibrium dialysis at 37° C for 5.5 h against isotonic Sörensen phosphate buffered saline, pH 7.4. The dialysis cell contained 1 ml serum and 1 ml buffer, separated by a cellulose dialysis membrane (Cuprophane M150). Adsorption of the drug to the membrane was negligible. The coefficient of variation over the concentration range 0.03 – 0.3 mg l^{-1} was 4.2%. The area under the concentration-time curve during a dose interval of 12 h, AUC (0,12), was estimated using the linear trapezoidal rule. Total body clearance/bioavailability (CL/*F*) was calculated as: dose (500 mg)/AUC (0,12) and expressed in ml min^{-1} or 1 min^{-1}. The elimination rate constant (λ) was obtained from the slope of the log-linear regression line through the last three time points in the dose interval. The elimination half-life $t_{½}$ was calculated from $\lambda^{-1} \cdot 0.693$. An apparent volume of distribution (*V*/*F*), corrected for individual body weight, was calculated from $CL/F \cdot \lambda^{-1}$ divided by the individual body weight. From the values of unbound serum naproxen concentrations identical calculations were performed to obtain the pharmacokinetic parameters for unbound naproxen: AUCu (0,12), CLu/*F*, $t_{½}$u and *V*u/*F*.

Statistical analysis

The means of the pharmacokinetic parameters in both groups were analysed for statistically significant differences with the two tailed *t*-test

Table 1 Measures of disease activity and drug therapy in eight patients with active rheumatoid arthritis during chronic therapy with naproxen 500 mg twice daily.

Patients *Age (years)*	*Sex*	*Hgb* (g/dl)*	*ESR† (mm h^{-1})*	*Morning stiffness (h)*	*Number of swollen joints*	*Number of tender joints*	*Comedication‡*
60	F	8.5	113	1	25	4	1,2
64	F	9.7	129	0.5	17	10	1,3
63	M	9.8	88	0	7	7	1,3
65	M	11.1	116	1	10	17	1,4,5,6,
55	F	11.0	56	1.5	13	6	1,5,7
63	F	9.9	77	0	9	9	1,5
65	F	9.9	80	2	9	5	8
61	F	8.5	80	2.5	28	30	8,9

* Hgb: haemoglobin, normal values: M: 14–18 g/dl; F: 12–16 g/dl.

† ESR: erythrocyte sedimentation rate (Westergren) normal value F: < 21 mm h^{-1}; M: < 10 mm h^{-1}.

‡ Comedication: 1. aurothioglucose, 2. oxazepam, 3. cimetidine, 4. alprenolol, 5. ferrous fumarate, 6. temazepam, 7. frusemide, 8. azathioprine, 9. prednisone.

for unpaired data. Results were expressed as mean ± s.d. unless otherwise stated.

Study ethics

The study was approved by the ethics committee of the University Hospital St Radboud. Patients gave verbal and volunteers written informed consent.

Results

The pharmacokinetic data of naproxen during chronic intake of 500 mg twice daily both for patients with active rheumatoid arthritis and the healthy male volunteers are listed in Table 2. The mean total and unbound serum naproxen concentration-time curves for patients with active rheumatoid arthritis and healthy male volunteers are shown in Figure 1. The serum naproxen concentrations at time 0 (C_{min}) and peak (C_{max}) were significantly lower in patients than in healthy volunteers (both $P < 0.0001$); also the AUC (0,12) was smaller in patients: 641 ± 101 mg l^{-1} h *vs* 896 ± 85 mg l^{-1} h ($P < 0.0001$). In the patient group there was a significantly larger *V/F* and CL/*F*, whereas $t_{½}$ was not different from that in the group of healthy volunteers. The unbound naproxen concentrations at C_{min} and C_{max} were significantly higher in patients than in healthy volunteers ($P < 0.02$ and $P < 0.01$ respectively); also the AUCu (0,12) was found to be greater: 1.9 ± 0.9 mg l^{-1} h *vs* 0.7 ± 0.2 mg l^{-1} h ($P < 0.01$). The values of CLu/*F* and *Vu/F* were significantly smaller in patients with active disease than in volunteers (both $P < 0.001$).

The values of *V/F* in both groups were negatively correlated with serum albumin concentration

Table 2 Pharmacokinetics (mean ± s.d.) of naproxen in eight patients with active rheumatoid arthritis and eight healthy male volunteers during chronic intake of naproxen 500 mg twice daily

		Total serum naproxen			*Unbound serum naproxen*		
		Patients	*Volunteers*	P	*Patients*	*Volunteers*	P
C_{max}	(mg l^{-1})	79 ± 12	110 ± 7	< 0.0001	0.42 ± 0.21	0.19 ± 0.07	< 0.02
C_{min}	(mg l^{-1})	38 ± 8	57 ± 7	< 0.0001	0.07 ± 0.02	0.03 ± 0.01	< 0.01
AUC (0,12)	(mg l^{-1} h)	641 ± 101	896 ± 85	< 0.0001	1.9 ± 0.9	0.7 ± 0.2	< 0.01
CL/F	(ml min^{-1})	13.3 ± 2.5	9.4 ± 0.9	< 0.001			
	(l min^{-1})				5.3 ± 2.5	11.9 ± 2.7	< 0.001
V/F	(l kg^{-1})	0.18 ± 0.03	0.11 ± 0.01	< 0.0001	26 ± 13	72 ± 27	< 0.001
$t_{½}$	(h)	10.4 ± 2.0	10.0 ± 1.8	NS	3.6 ± 0.8	4.8 ± 0.8	< 0.02

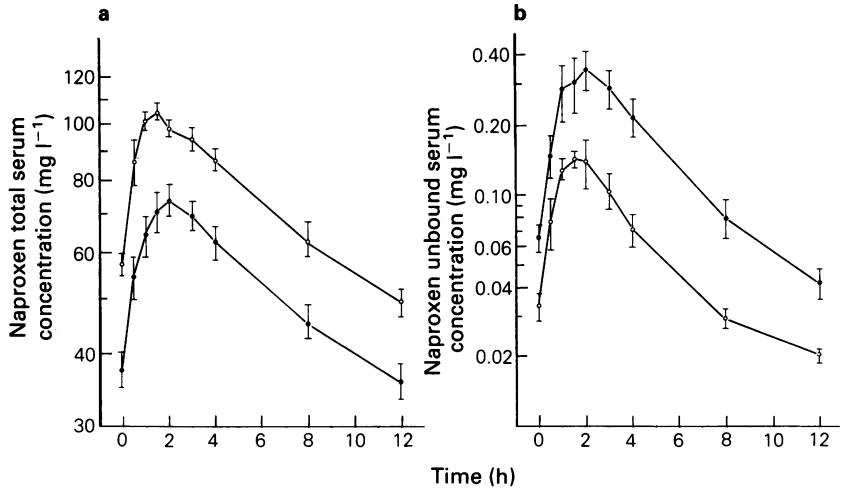

Figure 1 Serum naproxen concentration-time curves in eight patients with active rheumatoid arthritis (●) and eight healthy male volunteers (○) for total (a) and unbound drug (b) over one dose interval during chronic intake of 500 mg naproxen twice daily. Bars indicate the s.e. mean.

($r = -0.85$; $P < 0.001$). The values of CL/*F* in both groups were also inversely correlated with serum albumin concentration ($r = -0.76$, $P < 0.001$).

The recovery of naproxen and desmethylnaproxen conjugates, excreted in the urine during the 12 h dose interval was similar in the patients and the volunteers (1.2 ± 0.2 mmol and 1.3 ± 0.1 mmol naproxen equivalents, respectively). These values represented 54% and 59% of the oral naproxen dose during chronic intake in patients and volunteers, respectively.

Discussion

In the group of eight patients with active rheumatoid arthritis the value of AUC (0,12) was 72% that in eight healthy male volunteers during one dose interval of 12 h on chronic treatment with naproxen 500 mg twice daily. All subjects took the morning dose of 500 mg with breakfast, which is known not to interfere with the completeness of drug absorption (Segre, 1975). Any other medication in the patient group was either omitted or given at a later time to avoid a possible interaction with naproxen absorption. In healthy volunteers naproxen absorption after oral administration of a single dose up to 4000 mg is nearly complete. However, non-linear, decreasing increments of AUC have been observed upon administration of subsequent larger doses, probably due to saturation of albumin binding (Runkel *et al.*, 1974, 1976).

The similar renal excretion of drug equivalents in patients and volunteers in this study suggests an unchanged absorption of the drug in patients. For these reasons it is concluded that the smaller AUC (0,12) values in patients with rheumatoid arthritis were not the consequence of impaired absorption of naproxen in active disease.

The alterations of AUC (0,12), *V*/*F* and CL/*F* found in patients with active rheumatoid arthritis during chronic naproxen treatment are consistent with the pharmacokinetics of comparable compounds. The clearance of drugs with high albumin binding and a low extraction ratio is affected by changes in the unbound drug fraction, and an increase in the concentration of unbound drug thus results in a higher total clearance (Rowland, 1984). Both *V*/*F* and CL/F in the patients with active disease were 40–60% higher than the corresponding values in healthy volunteers. Therefore, with regard to the equation $t_{½} = 0.693\ V/CL$, little difference in $t_{½}$ between the two groups is expected.

The clinical consequences of higher unbound concentrations of naproxen in patients with active rheumatoid arthritis are unclear. In general, increases in unbound drug may change a therapeutic concentration into a toxic one. Data on the possible relation of the occurrence of side effects in patients with high unbound naproxen concentration are not available. Neither the incidence nor the severity of side effects has so far been found to increase during treatment of patients with rheumatoid arthritis with dosages as high as 1500 mg naproxen daily (Day *et al.*, 1982; Hazleman *et al.*, 1979; Mowat *et al.*, 1984).

On the other hand, the increase in unbound naproxen concentration especially in patients with more active disease might be beneficial if the anti-inflammatory effects of naproxen correlate with unbound drug concentration in the serum.

The differences found in CLu/*F* and *V*u/F between patients and healthy volunteers may result from multiple causes: e.g.: age, differences in sex distribution, and in the existence of rheumatoid arthritis. Upton *et al.* (1984) observed in elderly males (mean age 71 ± 4 years) during long-term naproxen administration a decrease by more than 50% of CLu/*F* compared with young males (29 ± 6 years), and also in the elderly a rise in unbound naproxen plasma concentrations. A similar difference in age exists between the patients (62 ± 3 years) and volunteers (24 ± 3 years) in this study. Apart from the age-related factors, disease activity in patients with rheumatoid arthritis may have implications. The same group of patients will be re-examined as soon as a remission of rheumatoid arthritis or a major improvement in disease activity has been achieved to study disease-related changes in naproxen pharmacokinetics.

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